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Yield: 100%

¹H NMR (CDCl₃): 1.1-1.3 (m, 2H); 1.45 (s, 9H); 1.4-1.5 (m, 1H); 1.55-1.75 (m, 4H); 2.33 (t, 2H); 2.6-2.75 (m, 2H); 3.45 (m, 2H); 3.61 (m, 2H); 3.67 (m, 4H); 4.0-4.2 (m, 1H).

5 **84** (1.54 g; 2.45 mmol) in solution in dioxan (15ml) was treated with 12N HCl (4ml) at 0°C; After stirring at ambient temperature for 2 hours, the mixture was evaporated and triturated in ether to give **85** as a solid.

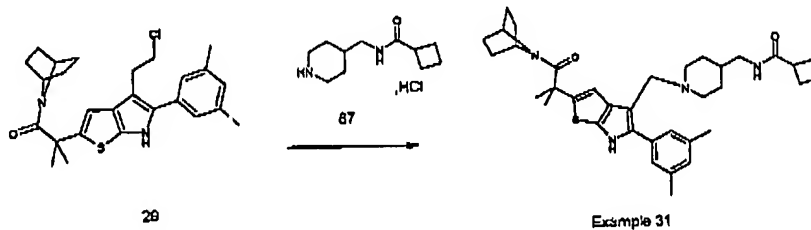
Yield: 100%

¹H NMR (DMSO): 1.28-1.34 (m, 2H); 1.42-1.45 (m, 3H); 1.79 (d, 2H); 2.32 (t, 2H); 2.7-2.85 (m, 2H); 3.20 (d, 2H); 3.41 (m, 4H); 4.5-4.6 (m, 4H); 8.71 (m, br, NH).

Example 31

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-

4-[4-(cyclobutylcarbonylaminomethyl)piperidin-1-ylmethyl]-5-(3,5-dimethylphenyl)-

15 **6H-thieno[2,3-*b*]pyrrole**

A mixture of **29** (0.115 g; 0.25 mmol), **87** (0.116 g, 0.5 mmol), K₂CO₃ (0.07 g; 0.5 mmol) in acetonitrile (2 ml) and DMF (0.5 ml) was heated at 85°C for 3 hours under argon atmosphere. The crude mixture was purified by flash chromatography eluting successively with AcOEt / methylene chloride 50/50, AcOEt and 3.5 N NH₃ in MeOH / AcOEt 10 / 90 to give after trituration in ether/pentane **Example 31** as a solid.

Yield: 90 %

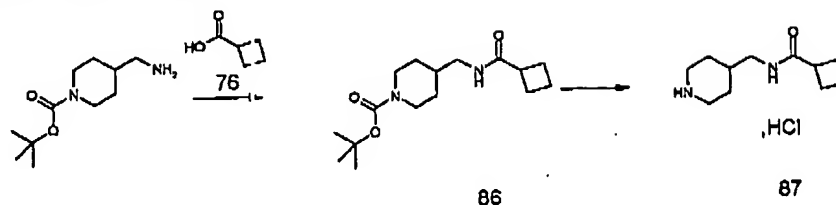
¹H NMR (CDCl₃) (δ ppm) 1.26 – 1.32 (m, 6H); 1.45 – 1.75 (m, 8H); 1.61 (s, 6H); 1.8 – 2.3 (m, 8H); 2.34 (s, 6H); 2.6 – 2.75 (br s, 2H); 2.9 – 3.15 (m, 6H); 4.1 (br s, 1H); 4.75 (br s, 1H); 5.45 (br s, 1H); 6.72 (s, 1H); 6.944 (s, 1H); 7.058 (s, 2H); 8.19 (s, 1H).

MS-ESI: 615 [M+H]⁺

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The starting material was prepared as follows:



1-tert-butoxycarbonyl-4-aminomethyl piperidine (0.645 mg; 3 mmol) was added, under argon atmosphere to a stirred solution of cyclobutane carboxylic acid (0.3g; 3 mmol), EDC (0.864g; 5 4.5 mmol), DIEA (0.78ml; 4.5 mmol) and DMAP (0.055g; 0.45 mmol) in methylene chloride (30 ml). The mixture was stirred overnight, evaporated and purified by flash chromatography, eluting successively with methylene chloride, AcOEt and 3.5 N NH₃ in MeOH / AcOEt 10 /90 to give 77 as a solid.

Yield : 56%

10 ¹H NMR (CDCl₃) 1.23 (m, 2H); 1.44 (s, 9H); 1.61–1.65 (m, 3H); 1.80–2.30 (ms, 6H); 2.68 (br s, 2H); 2.98 (m, 1H); 3.12 (br s, 2H); 4.12 (br s, 2H); 5.42 (br s, 1H).

86 (0.44g; 1.35 mmol) was dissolved in dioxan (3 ml) and treated with a solution made of 12N HCl / dioxan 5/25 (3 ml). The mixture was heated at 55°C under argon atmosphere 15 overnight. After evaporation to dryness, the residue was triturated in a mixture of MeOH, methylene chloride and ether to give 87 as solid.

Yield: 69%

¹H NMR (DMSO-d₆) 1.25 (m, 2H); 1.60–1.80 (m, 4H); 1.87 (m, 1H); 1.99 (m, 2H); 2.08 (m, 2H); 2.77 (m, 2H); 2.80–3.05 (m, 3H); 3.37 (m, 2H).

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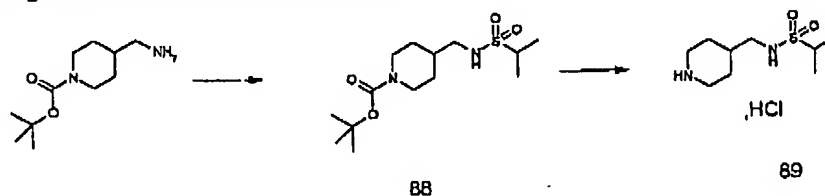
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Example 32 was prepared following a method described in Example 31.

Yield: 88%

¹H NMR (CDCl₃): 1.25–1.40 (m, 4H); 1.38 (d, 6H); 1.45–1.80 (m, 7H); 1.62 (s, 6H); 1.90–2.10 (br s, 2H); 2.35 (s, 6H); 2.6–2.80 (br s, 2H); 2.90–3.15 (m, 8H); 3.15 (s, 1H); 4.10 (br s, 2H); 4.75 (br s, 1H); 6.75 (s, 1H); 6.95 (s, 1H); 7.05 (s, 2H); 8.16 (s, 1H).
MS-ESI: 639[M+H]⁺

The starting material was prepared as follows:



10 Isopropylsulfonyl chloride (0.230 ml; 2.05 mmol) was added under argon atmosphere at 0°C to a solution of 1-(4-aminomethylpiperidin-1-yl)propan-1-one (0.4g; 1.87 mmol) and K₂CO₃ (0.285 g; 2.05 mmol) in acetonitrile (15 ml). The mixture was stirred overnight at ambient temperature and purified by flash chromatography eluting successively with methylene chloride, AcOEt / methylene chloride 80/20 to give 88 as a solid.

15 Yield : 41%

¹H NMR (CDCl₃) 1.13 (m, 2H); 1.38 (d, 6H); 1.45 (s, 9H); 1.60–1.80 (m, 3H); 2.68 (br s, 2H); 3.04 (m, 2H); 3.16 (m, 1H); 4.06–4.20 (br s, 3H).

20 **88** (0.340g; 0.94 mmol) was dissolved in dioxan (3 ml) / methylene chloride (0.3 ml) and treated with a solution made of 12N HCl / dioxan 5/25 (2 ml). The mixture was stirred at ambient temperature under argon atmosphere overnight. After evaporation to dryness, the residue was triturated in a mixture of MeOH, methylene chloride and ether to give **89** as solid.

Yield: 100%

25 ¹H NMR (CDCl₃) 1.35 (d, 6H); 1.66 (m, 2H); 1.81 (br s, 1H); 1.92 (m, 2H); 3.08 (m, 2H); 3.17 (m, 1H); 3.51 (m, 2H).

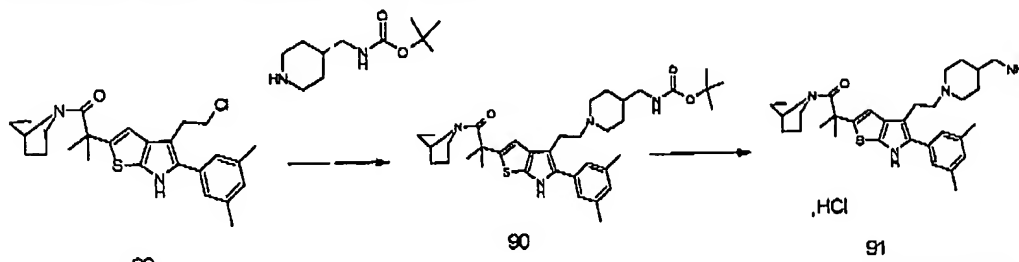
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^1H NMR (CDCl_3) : 1.22 (d, 6H); 1.20-1.35 (m, 6H); 1.45-1.85 (m, 7H); 1.60 (s, 6H); 2.01 (br s, 2H); 2.35 (s, 6H); 2.66 (br s, 2H); 2.90-3.12 (m, 6H); 4.10 (br s, 1H); 4.67 (m, 2H); 4.89 (m, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.13 (s, 1H).
MS-ESI: 619[M+H] $^+$

5

The starting material was prepared as follows:



A mixture of 29 (3.27 g; 7.2 mmol), 4-tert-butoxycarbonylaminomethyl piperidine (03.08 g, 14.2 mmol), K_2CO_3 (1.95 g; 14.2 mmol) in acetonitrile (50 ml) and DMF (0.5 ml) was heated at 85°C for 3 hours under argon atmosphere. The crude mixture was purified by flash chromatography eluting successively with AcOEt / methylene chloride 50/50, AcOEt and 3.5 N NH_3 in MeOH / AcOEt 20 / 80 to give 90 as a solid.

Yield: 80 %

^1H NMR (CDCl_3) 1.26-1.40 (m, 6H); 1.44 (s, 9H); 1.45-1.75 (m, 7H); 1.59 (s, 6H); 2.00 (m, 2H); 2.35 (s, 6H); 2.66 (m, 2H); 2.93-3.49 (ms, 6H); 4.10 (br s, 1H); 4.61 (br s, 1H); 4.75 (br s, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.13 (s, 1H).

90 (3.06g; 4.84 mmol) was dissolved in dioxan (13 ml) and treated with a solution made of 12N HCl / dioxan 5/25 (9.7 ml). The mixture was stirred at ambient temperature under argon atmosphere overnight. After evaporation to dryness, the residue was triturated in a mixture of MeOH, methylene chloride and ether to give 91 as solid.

Yield: 100%

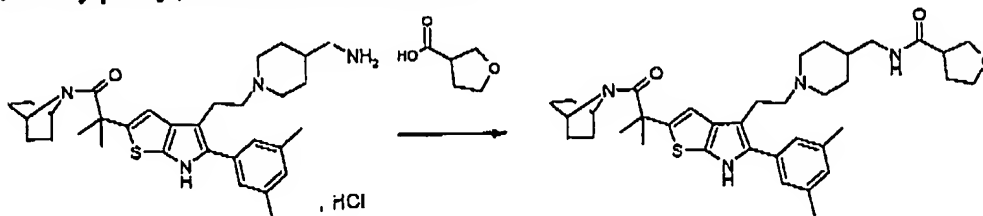
^1H NMR ($\text{DMSO}-d_6$) 1.26-1.45 (m, 6H); 1.40-1.70 (m, 7H); 1.52 (s, 6H); 1.80-2.00 (m, 3H); 2.00 (m, 2H); 2.34 (s, 5H); 2.66 (m, 2H); 3.60 (m, 2H); 4.1 (br s, 1H); 4.55 (br s, 1H); 4.75 (br s, 1H); 6.95 (s, 1H); 6.98 (s, 1H); 7.10 (s, 2H); 8.07 (s, 1H).

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Example 34

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-
4-[2-(4-{tetrahydrofuran-2-yl-carbonylaminoethyl}piperidin-1-yl)ethyl]-5-(3,5-
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole



91

Example 34

To a suspension of tetrahydro-3-furoic acid (0.029 g; 0.25 mmol) in methylene chloride (2 ml), was added DIEA (0.190 ml; 1.09 mmol), HATU (0.104 g; 0.275 mmol) and 91 (0.146 g; 0.25 mmol). The mixture was stirred at ambient temperature overnight. The crude mixture was purified by flash chromatography eluting successively with AcOEt/ methylene chloride 50/50 and 3.5 N NH₃ in MeOH/AcOEt 5 / 95 to give Example 34 as a solid.

Yield: 83%

¹H NMR (CDCl₃) : 1.20–1.45 (m, 6H); 1.45–1.85 (m, 7H); 1.61 (s, 6H); 2.00 (m, 2H); 2.16 (m, 2H); 2.34 (s, 6H); 2.64 (m, 2H); 2.90 (m, 3H); 3.01 (m, 2H); 3.16 (t, 2H); 3.80 (m, 1H); 3.90 (m, 2H); 3.94 (m, 1H); 4.10 (br s, 2H); 4.75 (br s, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.05 (s, 2H); 8.15 (s, 1H).

MS-ESI: 631[M+H]⁺**Examples 34.1–34.6**

Following a procedure similar to that described in Example 34, the compounds of table 34 were prepared.

Table 34

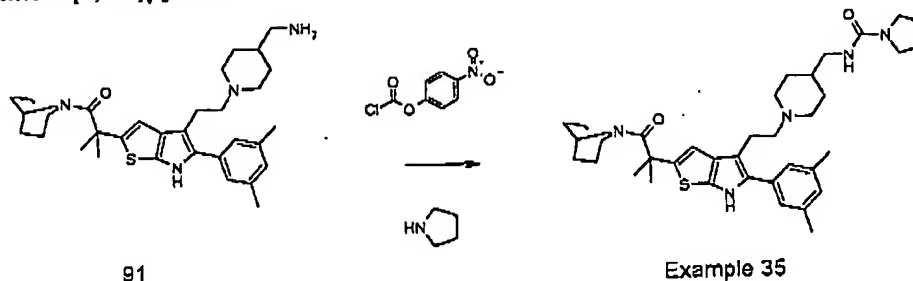
Example		MS-ESI
34.1		671 [M+H] ⁺

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Example 35

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-
4-[2-(4-{pyrrolidin-1-ylcarbonylmethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-
thieno[2,3-b]pyrrole



5 4-nitrophenylchloroformate (0.056 g; 0.275 mmol) was added under argon atmosphere, at 0°C to a solution of 91 (0.250 g; 0.25 mmol) and triethylamine (0.074 ml; 0.525 mmol) in methylene chloride (3 ml); after stirring at ambient temperature for 1 hour, pyrrolidine (0.023 ml) was added. The mixture was stirred at ambient temperature overnight, evaporated to dryness and purified by flash chromatography eluting with 3.5 N NH₃ in MeOH / methylene chloride 6/94 to give example 35 as a solid.

Yield : 78%

¹H NMR (CDCl₃) : 1.20–1.35 (m, 4H); 1.45–1.75 (m, 4H); 1.64 (s, 6H); 1.45–1.95 (m, 10H); 2.03 (m, 2H); 2.36 (s, 6H); 2.60 (m, 2H); 3.12 (m, 2H); 3.18 (m, 6H); 3.54 (m, 2H);
15 4.18 (br s, 1H); 4.70 (br s, 1H); 6.90 (s, 1H); 6.93 (s, 1H); 7.03 (s, 2H); 8.55 (s, 1H).

Examples 35.1–35.4

Following a procedure similar to that described in Example 35, the compounds of table 35 were prepared.

20

Example		MS-ESI
35.1		618 [M+H] ⁺